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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/980,771	01/10/2002	Christophe D'Hulst	410.020	7483

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EXAMINER	
RAO, MANJUNATH N	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 10/15/2003 18

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/980,771	Applicant(s) D'HULST ET AL.	
	Examin r Manjunath N. Rao, Ph.D.	Art Unit 1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 July 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10 January 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 12-14 are currently pending in this application.

Election/Restrictions

Applicants election of group IV, claims 12-14 with traverse is acknowledged. The traversal is based on applicants argument that there is a single inventive concept under PCT Rule 13.1 and since there was no restriction requirement in the PCT application. While such arguments are not persuasive to overcome the restriction, applicant's cancellation of all remaining non-elected claims renders such arguments moot. Claims 12-14 are now under consideration.

Priority

Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d).

Drawings

Drawings submitted in this application are accepted by the Examiner for examination purposes only.

Sequence Compliance

Applicant is required to comply with the sequence rules by inserting the sequence identification numbers of all sequences recited within the claims and/or specification. For example, it is particularly noted that applicants fail to provide appropriate SEQ ID NO to

sequences depicted in the figures and also to sequences recited in the specification (see for example page 10 or 13). See particularly 37 CFR 1.821(d).

Claim Objections

Claim 14 is objected to because of the following informalities: Claim 14 recites the pharmaceutical composition as "containing at least one polypeptides". As can be seen the phrase is grammatically improper. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 12-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The scope of claims 12 and 14 appear to be the same. It is not clear to the Examiner as to how claim 14 differs from 12 in the scope. It appears that applicants are trying to make a distinction between the claims using the phrase "comprising of" and "containing at least". However, use of these two phrase does not change the scope of the claims. Examiner suggests the use of the phrase "consisting of" in claim 14 if applicants are intending to claim the subject matter of claim 12 with a difference in scope.

Claim 13 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as

the invention. Claim 13 recites the phrase "several tens of μm". The metes and bounds of the phrase is not clear to the Examiner. Specifically it is not clear to the Examiner as to the range intended by the applicants with respect to the word "several", rendering the claim indefinite.

Claims 12-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 12 and 14 recite the phrase "especially by suppression". It is not clear to the Examiner as to what applicants mean by "suppression of an amino acid" or how those skilled in the art can "suppress" an amino acid in an amino acid sequence. Correction is required.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 12-14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a pharmaceutical composition comprising or consisting of a fusion protein wherein the fusion protein comprises or consists of a starch synthase fused to a heterologous protein of interest with a therapeutic effect to its C-terminal encoded by a chimeric polynucleotide sequence, does not reasonably provide enablement for a pharmaceutical composition comprising a fusion protein wherein the fusion protein comprises a variant starch synthase derived from starch synthase by amino acid addition, deletion or substitution, having the property of migrating to the site of starch granule biosynthesis in plant cells and of attaching to starch granules. The specification does not enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 12-14 are so broad as to encompass a fusion protein comprising any variant, mutant or recombinant starch synthase or any variant polypeptide having the property of migrating to the site of starch granule synthesis or attaching to starch granules irrespective of it having starch synthase activity. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of starch synthase polypeptides broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity, requires a knowledge of and guidance with regard to which specific amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the nucleotide and encoded amino acid sequence of only a single starch synthase enzyme. It would require undue experimentation of the skilled artisan to make and use the claimed polypeptides. The specification is limited to

teaching the use of a single starch synthase but provides no guidance with regard to the making of variants and mutants or with regard to other uses or with regard to making of proteins which simply have the capacity to migrate to the starch granule synthesizing site or to simply bind to starch granule. In view of the great breadth of the claim, amount of experimentation required to make the claimed polypeptides, the lack of guidance, working examples, and unpredictability of the art in predicting function from a polypeptide primary structure (e.g., see Ngo et al. in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495, Ref: U, Form-892), the claimed invention would require undue experimentation. As such, the specification fails to teach one of ordinary skill how to use the full scope of the polypeptides encompassed by this claim.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompasses fusion proteins comprising all modifications and fragments of any starch synthase or fusion protein wherein the fusion protein comprises a variant starch synthase derived from starch synthase by amino acid addition, deletion or substitution, having the property of migrating to the site of starch granule biosynthesis in plant cells and of attaching to starch granules

because the specification does not establish: (A) regions of the protein structure which may be modified without affecting activity; (B) the general tolerance of starch synthases to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residue with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including fusion proteins comprising enormous number of amino acid modifications of starch synthases. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of starch synthases having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claims 12-14 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 12-14 are directed to fusion polypeptides comprising starch synthases and variants of starch synthases. Claims 12-14 are rejected under this section of 35 USC 112

because the claims are directed to a genus of polypeptides including modified polypeptide sequences, modified by at least one of deletion, addition, insertion and substitution of an amino acid residue that have not been disclosed in the specification. No description has been provided of the modified polypeptide sequences encompassed by the claim. No information, beyond the characterization of a single fusion polypeptide has been provided by applicants which would indicate that they had possession of the claimed genus of modified polypeptides. The specification does not contain any disclosure of the structure of all the polypeptide sequences comprising the starch synthase portion of the fusion polypeptide, including fragments and variants within the scope of the claimed genus. The genus of polypeptides claimed is a large variable genus including peptides which can have a wide variety of structures. Therefore many structurally unrelated polypeptides are encompassed within the scope of these claims. The specification discloses only a single species of the claimed genus which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that applicant had possession of the claimed invention at the time the instant application was filed.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claim Rejections - 35 USC § 102/103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 12-14 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Keeling et al. (WO 98/14601, 4-9-1998). Claims 12-14 are drawn to a pharmaceutical composition comprising a fusion protein wherein the fusion protein comprises a heterologous polypeptide with a therapeutic property fused to the C-terminal of starch synthase polypeptide or its variant capable of binding to starch granule or migrate to the site of starch granule biosynthesis, wherein said fusion polypeptide is encoded by a polynucleotide, wherein the composition comprises physiologically acceptable vehicle, wherein the diameter of starch granule is 0.1-10 μm and the proportion of starch by weight is between 0.1 and 1.0%. Keeling et al. disclose what they call as "starch encapsulated protein" comprising a fusion protein consisting of a starch synthase capable of binding to starch granule or migrate to the site of starch granule biosynthesis, fused through its C-terminal, to a heterologous peptide or polypeptide, wherein the heterologous peptide or polypeptide is a hormone or enzyme or proteinaceous medicine (i.e., has a therapeutic property) etc (see page 19). The reference does not specifically disclose the composition as a "pharmaceutical composition", or that the starch granule diameter is 0.1-10 μm and the proportion of starch by weight is between 0.1 and 1.0%. However, as the reference discloses starch encapsulated proteins comprising a fusion polypeptide

of starch synthase and a proteinaceous medicine, Examiner takes the position that the reference anticipates claims 12 and 14 as written. While the reference does not specifically disclose the size or the percent by weight of the starch granule in the composition, Examiner takes the position that the composition disclosed in the reference inherently has said dimensions and % weight thereby anticipating claim 13 as well (Since the Office does not have the facilities for examining and comparing applicants' starch granule with the starch granule of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the starch granule of the prior art does not possess the same material structural and functional characteristics of the claimed protein). See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *In re Fitzgerald* et al., 205 USPQ 594.)

Alternatively, if one skilled in the art argues that the above reference does not anticipate, it would have been obvious to those skilled in the art, with the teachings of Keeling et al. in hand, to take the same composition taught by Keeling et al. and claim it as a "pharmaceutical composition". One of ordinary skill in the art would have been motivated to do so as Keeling et al. teach that said composition can be used to deliver "proteinaceous medicines" (i.e., polypeptides with therapeutic properties) through the intestines and teaches that said composition can be used for medicating an animal or providing hormones such as growth factors or for vaccination of an animal or for enhancing the nutrients available to an animal. It is well recognized that there is a commercial demand for various ways of drug delivery to humans and animals. One of ordinary skill in the art would have a reasonable expectation of success since Keeling et al. clearly demonstrate the use of their product for the above purpose and various

other purposes except for calling said composition as "pharmaceutical composition". Therefore, the above invention would have been *prima facie* obvious to those skilled in the art.

Conclusion

None of the claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Manjunath N. Rao, Ph.D. whose telephone number is 703-306-5681. The examiner can normally be reached on 7.30 a.m. to 4.00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached on 703-308-3804. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-306-0196.

MANJUNATH RAO
PATENT EXAMINER

Manjunath N. Rao
October 9, 2003